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Summary Technical Report

Application of Near Infrared Spectroscopy, Intravascular Ultrasound and the Coronary Calcium Score to Predict Adverse Coronary Events

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ABSTRACT

Since the award date, the original pre-proposal has undergone a series of revisions under the direction of officials at TATRC.

These revisions have included changes in investigational design, period of the study, data collection and analysis.

In June of 2012, the revised protocol (attached) was approved by Dr. Jeffrey Stephenson for submission to the local institutional review board in July.

Approval was granted (attached) and second level review for human protections was requested. Implementation of the study will commence following that approval. The design of the study includes a minimum of three years of patient follow-up.

Anticipating this, a four year no cost extension is being requested to complete the project.

Application of Near Infrared Spectroscopy, Intravascular Ultrasound and the Coronary Calcium Score to Predict Adverse Coronary Events

Principal Investigator: Charles R. Lambert, M.D., Ph.D., M.B.A. [1]
Sponsor: Department of Defense (DOD) Telemedicine and Advanced Technology Research Center (TATRC)
Study Site: Florida Hospital Pepin Heart Institute[2], Dr. Kiran C. Patel Research Institute[3]

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[1] Dr. Lambert has academic appointments at the University of Florida and the University of South Florida and is employed full time as Medical Director of Florida Hospital Pepin Heart Institute and the Dr. Kiran C. Patel Research Institute.

[2] This work will be performed at Florida Hospital Pepin Heart Institute fka University Community Hospital and Pepin Heart Hospital.

[3] The Dr. Kiran C. Patel Research Institute is the research department of Florida Hospital Pepin Heart Institute.

[3] The Dr. Kiran C. Patel Research Institute is the research department of Florida Hospital Pepin Heart Institute.

Technical Abstract

Background: Cardiovascular disease is the leading cause of death in the United States and other industrialized countries. Coronary artery disease is responsible for the majority of that mortality and associated morbidity. A major target of past research has been development of methods to screen at risk individuals for future cardiac events. The Prospective Army Coronary Calcium Study (PACC) targeted this problem using electron beam computed tomography (EBCT) to detect coronary artery calcium (CAC) [1-4]. Recently, near infrared spectroscopic catheter technology (NIRS) has become available for use in humans to detect lipid in the coronary arteries. This is felt to be of primary importance in the vulnerable plaque hypothesis for precipitating coronary events [5]. It is unknown whether NIRS is useful in screening at risk individuals for future cardiac events.

Objective/Hypothesis: This proposal will compare NIRS, CAC, intracoronary ultrasound (IVUS), and angiographic findings in patients referred for cardiac catheterization as predictors for future cardiac events

Study Design: Patients referred for diagnostic cardiac catheterization will be considered for inclusion in the study. Following informed consent, standard left heart catheterization will be augmented with study of the proximal coronary arteries using a combination NIRS/IVUS catheter that is FDA approved for the use described in this proposal. Registered angiographic and IVUS images, as well as NIRS chemograms will be recorded. Patients will subsequently undergo CAC scoring using EBCT and standard technique as defined in PACC. Five-year outcome data will be obtained through clinical and telephone follow-up. Cardiac outcomes will be related to CAC, IVUS, NIRS and angiographic findings using Cox proportional hazard modeling.

Relevance: This study has direct relevance to the Army's Cardiovascular Screening Program (CVSP), screening of individuals in high-risk occupations as well as to the population in general. The utility of NIRS imaging in predicting cardiovascular events has not been tested, either alone, or compared to other invasive and non-invasive modalities.

Statement of Work

Year One

- Hire new personnel dedicated to the project
- Acquire NIRS console
- Train staff and physicians
- Establish inventory of associated supplies
- Establish image archival system and database
- Implement standard operating procedures
- Enroll patients with a total target of 230
- Outcomes follow-up on enrolled patients
- Ongoing data analysis

Year Two

- Enroll patients with a total target of 230
- Outcomes follow-up on enrolled patients
- Ongoing data analysis
- Interim analysis

Year Three

- Enroll patients with a total target of 230
- Outcomes follow-up on enrolled patients
- Ongoing data analysis
- Interim analysis

Year Four

- Outcomes follow-up on enrolled patients
- Ongoing data analysis
- Interim analysis

Year Five

- Outcomes follow-up on enrolled patients
- Ongoing data analysis
- Interim analysis

Background

Cardiovascular disease is the leading cause of death in the United States and other industrialized countries. Coronary artery disease is responsible for the majority of that mortality and associated morbidity. A major target of past research has been development of methods to screen at-risk individuals for asymptomatic coronary artery disease or to assess patients with known disease. This work has yielded a number of noninvasive tests with varying sensitivity and specificity that are widely used in clinical practice. The Prospective Army Coronary Calcium Study (PACC) targeted this problem using electron beam computed tomography (EBCT) to assess coronary artery calcium (CAC) [1-4].

When screening tests, such as CAC, are positive in an individual patient, the evaluating physician will usually review those results and decide whether or not to proceed to invasive testing. If indicated, invasive testing most often includes cardiac catheterization. This serves to define the coronary artery anatomy, left ventricular function, and the presence or absence of any flow limiting stenoses. These data serve to guide therapy that may include medication, surgery, and or percutaneous coronary intervention. In addition, they are important guides to medical waivers for duty and other occupational or professional guidance.

Although this approach has become standard, it only offers definitive diagnosis and treatment guidance for fixed obstructive coronary artery lesions. Contemporary research has shown that a significant proportion of myocardial infarctions may occur in patients with minimal or no coronary artery disease on angiography. These observations, as well as post mortem pathologic studies, have led to the concept of the vulnerable plaque as an important pathophysiological mechanism in the transition of a stable patient to an unstable one [6-8].

Although CAC as used in PACC is predictive of coronary events, power varies widely [9]. Routine studies such as CAC or even angiography offer little in identifying patients with vulnerable plaques [10, 11].

The vulnerable plaque appears to be comprised of a lipid pool in the wall of the artery that, as suggested above, may or may not be associated with obstructive coronary artery disease. This pool is usually covered with a thin fibrous cap vulnerable to a variety of influences that may cause rupture and exposure of underlying thrombogenic material to flowing blood. This pool cannot be distinguished on angiography or even intracoronary ultrasound. Plaque rupture usually leads to acute thrombosis resulting in an acute coronary syndrome and myocardial infarction.

Appreciation of the importance of identifying the vulnerable plaque has led to a great deal of research. Both invasive and noninvasive techniques have been used in an attempt to define more detail with regard to plaque composition than is available from routine angiography alone [10].

Promising in the array of techniques currently under investigation is the technique of near infrared spectroscopy (NIRS) [5, 12-16].

NIRS utilizes catheter-based reflectance spectroscopy at the time of cardiac catheterization to yield a chemogram that can be precisely correlated with the contrast angiogram as well as intravascular ultrasound images (IVUS). A reflectance catheter is introduced into the coronary artery at the time of catheterization using a standard guide catheter and intracoronary guidewire. With pullback of the catheter, near-infrared spectral data is collected in 360 degrees and processed in an anatomic format. The chemogram reveals areas in the coronary artery wall and in atherosclerotic lesions that contain pools of cholesterol and related compounds. These areas are felt to represent the nidus of the vulnerable plaque.

This methodology has been extensively validated in vitro and on human coronary artery specimens and has been FDA approved for use in humans to detect abnormalities in the coronary arteries. Such abnormalities include, but are not limited to, pools of lipid, stenosis and structural changes seen on ultrasound. Identification of lipid pools using this technology has been predictive of peripheral cholesterol embolization during percutaneous intervention as well as the no reflow phenomenon [17]. These observations highly support its utility in identifying potential vulnerable plaque in both patients with obstructive and non-obstructive coronary disease.

Clinical outcomes of patients with positive chemograms using NIRS have not been documented or compared with other methods.

Hypotheses

- NIRS detection of lipid pools in coronary arteries is predictive for adverse cardiovascular outcomes in patients referred for diagnostic cardiac catheterization.

- NIRS detection of lipid pools in coronary arteries is superior to CAC, IVUS, angiographic and Framingham risk score predictors.

Technical Objectives

- To define the prevalence of NIRS detected lipid pools in patients referred for coronary angiography.
- To relate the prevalence of obstructive coronary disease defined by angiography to the prevalence of NIRS detected lipid pools in the same patient.
- To relate the prevalence of CAC defined by EBCT to the prevalence of NIRS detected lipid pools in the same patient.
- To relate coronary morphology as defined by IVUS to the prevalence of NIRS detected lipid pools in the same patient.
- To compare the predictive value of the Framingham Risk Score, NIRS detected lipid pools, CAC defined by EBCT, coronary morphology as defined by IVUS, and coronary angiographic morphology for adverse cardiac events.

Project Milestones

- Year One Quarter One: Assigning study personnel, acquisition of equipment, physician and staff training and implementation of standard operating procedures for the study.
- Year One Quarter Two: Active recruitment begins.
- Year Two: Meeting recruitment goals and interim data analysis.
- Year Three: Completion of recruitment, interim data analysis and continued long-term follow-up.
- Years Four and Five: Follow-up.

Military Significance

Cardiovascular disease has long been an important issue for the Armed Forces of the United States [1-4, 18-21]. This stems, not only from the incidence and prevalence of the disease, but also the importance of screening servicemen and women in hazardous duty, high stress environments, and mission-critical positions. An integral part of aviation medical screening and that for the astronaut corps involves cardiovascular function.

As currently implemented, algorithms for cardiovascular military clearance rely on noninvasive testing leading to possible cardiac catheterization. These have been referred to above.

Although a significant number of active duty personnel undergo cardiac catheterization, no prospective screening for detection of vulnerable plaque by near infrared spectroscopy or other techniques is being used.

Detection of these coronary lesions may offer significant value in guiding therapy for such individuals, determining their mission readiness, and protection of military resources. This may prove of special value in aeromedical evaluation.

This project is an observational study that will relate the presence or absence of vulnerable plaque as detected by near infrared spectroscopy to adverse cardiac outcomes. This has special relevance to screening individuals in high-risk occupations such as aeromedical evaluation of pilots.

Public Purpose

Military application, as defined above, applies to the general public without modification due to the previously mentioned importance of coronary artery disease in the population at large.

Methods

The study involves utilization of an FDA approved intra-coronary near infrared spectroscopy unit in the setting of clinically indicated cardiac catheterization. These patients will receive spectroscopic study as well as standard angiography. Studies will be done in the cardiac catheterization laboratories of Florida Hospital Pepin Heart Institute. Institutional Review Board approval and informed consent from all patients will be obtained.

Recruitment of Patients and Screening

This is a single center observational study at Florida Hospital Pepin Heart Institute and the Dr. Kiran C. Patel Research Institute in Tampa, Florida.

Patients for this study will be recruited from those referred for elective diagnostic cardiac catheterization at PHH. As is current practice for the institution, inpatients and outpatients who may be candidates for research will be screened during daily research rounds by research coordinators and the principal investigator. The local IRB will be asked for Partial Waiver of Authorization to use protected health information (PHI) for screening using

the catheterization laboratory log. Screening activity is recorded using the screening log in the appendix.

If a patient is identified as a possible candidate for the study, the attending physician will be contacted for approval and, if given, the patient will be approached and educated regarding the study in the pre-procedural area or at the bedside for inpatients. Patients will be educated by Dr. Lambert and the associated clinical research coordinator. Informed consent will then be obtained.

Inclusion Criteria

1. Subject is at least 21 years of age.
2. Subject is scheduled for a clinically indicated left heart catheterization.
3. Subject is willing and able to provide informed consent prior to the index catheterization.
4. Use of the LipiScan™ system is not contraindicated.

Exclusion Criteria

1. Subject life expectancy at the time of cardiac catheterization is less than three years.
2. Subject is pregnant or suspected to be pregnant.

Cardiac Catheterization

Cardiac catheterization will be performed using standard technique. Following coronary angiography and left ventricular angiography, a 6 French guide catheter will be utilized for simultaneous IVUS and NIRS acquisition in the proximal to mid left anterior descending, circumflex, left main and right coronary arteries. These images will be obtained using standard laboratory protocol and stored for later archival.

NIRS and IVUS

The LipiScan™ and LipiScan™ IVUS Coronary Imaging System will be used for this study. This is the only available system for NIRS in humans. The console component of the LipiScan and LipiScan IVUS systems perform several functions. In brief, it provides (a) the near-infrared light source for spectroscopy, (b) a data-processing system that analyzes the signals returned from the catheter, (c) a user interface to the system, (d) a means of data storage, and (e) communication to the pullback device which drives the automated scanning of the catheter imaging core, (f) in the case of the LipiScan IVUS system. Additionally, the LipiScan IVUS console includes a piezo transducer to generate and receive acoustic energy for ultrasound.

Following pullback of the catheter through the artery, the system software displays a map in the form of a graphical representation indicating the likelihood that a lipid core containing plaque is present. This map is called a chemogram. It approximates an image of the artery as if viewed with a near-infrared camera from within the catheter. Additionally, the system software allows the operator to review previous patient procedures as well as store these procedures to CD/DVD for remote review or report generation.

The pullback rotation system (PBR) interfaces between the rotating catheter imaging core and the non-rotating components of the system. The catheter snaps into a socket on the face of the PBR, which completes the optical connections and allows for the unit to simultaneously actuate the inner imaging core and stabilize the catheter outer sheath. The longitudinal motion of the PBR permits only a distal-to-proximal automated pullback at a rate of 0.5 mm/sec. Manual movement of the imaging core is possible in either direction. The catheter core can be pulled back and rotated proximally over a total length of 15 cm.

The LipiScan™ IVUS Coronary Imaging Catheter is a single-use, disposable coronary catheter. The catheter is 3.2 F in diameter and 160 cm in usable length. The catheter is intended to be introduced into the vasculature via a 0.014- inch coronary guidewire, which is allowed to exit approximately 25 mm proximal to the distal tip. Two low-profile polymer markers are placed on the stiff proximal shaft to aid the user in locating the exit of the distal tip through the tip of a guiding catheter.

This system is in use for standard clinical evaluation of patients with coronary artery disease.

EBCT

For the measurement of CAC, EBCT will be performed using an Imatron C-150 LXP scanner calibrated daily with air and water phantoms. Images will be obtained using a 40- to 50-slice (3 mm thickness) protocol with image acquisition triggered to 60% to 80% of the electrocardiographic RR interval while respirations are held. Scans will be interpreted in a blinded manner using the Agatston scoring method.

EBCT will be performed when convenient for the patient but within 2 weeks of the index catheterization. This is related to the research and may be opted out of if the patient desires to participate only in the cardiac catheterization portion of the study.

Patient Follow-up

Patients will be followed by an experienced nurse coordinator using a structured interview process and the Seattle Angina Questionnaire (appendix). Adverse cardiac events will be corroborated with source documents whenever possible. Patients will be contacted by phone at 6 month intervals.

Outcome Events

1. Death from any cause
2. Cardiac death
3. Other cardiovascular death
4. Myocardial infarction
5. Percutaneous revascularization
6. Surgical revascularization
7. Heart failure
8. Re-hospitalization
9. Emergence of rhythm disturbances requiring treatment
10. Development of acute coronary syndrome
11. Cerebrovascular accident

Adverse events related to the study will include those temporally related to performance of the research procedure up to two weeks following the index cardiac catheterization. These will include coronary injury including dissection, perforation or occlusion, death, cerebrovascular accident, myocardial infarction and arrhythmia requiring treatment. All medications will be recorded at enrollment and follow-up points on the follow-up database form (appendix).

The patient data collection script for phone follow-up is included in the appendix.

Risks and Benefits

Patients included in this study are already undergoing clinically indicated cardiac catheterization with the inherent risks of that procedure. These include death, cerebrovascular accident, bleeding, infection, arrhythmia, access site damage, coronary dissection, coronary thrombosis and myocardial infarction, among others.

The risks of further coronary instrumentation with the Lipiscan™ IVUS Coronary Imaging Catheter are identical to those listed above, however, slightly higher in magnitude since a guidewire system is used to allow imaging within the arteries. The risk of any complication from procedures of this type is widely quoted as less than 1 in 1000 for experienced centers.

There is a slightly increased use of X-ray imaging used for the catheterization portion of the study and for EBCT if the patient does not opt out of that portion. Local IRB policy mandates estimation of that risk (see appendix for policy)[4].

Benefits from the imaging performed in this investigation may include prognostic information related to the likelihood of procedural complications from percutaneous coronary intervention, should one be performed[5]

Serious Adverse Event and Adverse Event Reporting

All unanticipated problems involving risk to subjects or others, serious adverse events related to participation in the study and subject deaths related to participation in the study should be promptly reported by phone (301-619-2165), by email (hsrrb@det.amedd.army.mil), or by facsimile (301-619-7803) to the USAMRMC, Office of Research Protections, Human Research Protection Office.

Local SAE requirements are included in the SAE reporting form included in the appendix. All local SAEs are to be reported using that form to the local IRB within 10 days of the event.

Additional Reporting Requirements

A complete written report will follow the initial notification. In addition to the methods above, the complete report will be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-ZB-PH, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

The protocol will be conducted in accordance with the protocol submitted to and approved by the ORP HRPO and will not be initiated until written notification of approval of the research project is issued by the ORP HRPO.

The knowledge of any pending compliance inspection/visit by the FDA, DHHS-OHRP, or other government agency concerning clinical investigation or research, the issuance of Inspection Reports, FDA Form 483, warning letters or actions taken by any Regulatory Agencies including legal or medical actions and any instances of serious or continuing noncompliance with the regulations or requirements will be reported immediately to ORP HRPO.

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[4] National Research Council. Health risks from exposure to low levels of ionizing radiation. BEIR VII Phase 2. Washington, DC: National Academies Press; 2006.

[5] Detection of lipid-coreplaques by intracoronary near-infrared spectroscopy identifies high risk of periprocedural myocardial infarction. Goldstein, J.A., Maini, B., Dixon, S.R, et al Circ Cardiovasc Interv 2011;4:429.

Data Analysis and Confidentiality

Accurate and complete study records will be maintained and made available to representatives of the U.S. Army Medical Research and Materiel Command. These representatives are authorized to review research records as part of their responsibility to protect human research volunteers. Research records will be stored in a confidential manner so as to protect the confidentiality of subject information

Data Storage and Case Report Forms

The case report form set for each individual patient will consist of the following:

1. Measurement Database Input Form
2. Copy of index cardiac catheterization report
3. Baseline Seattle Angina Questionnaire
4. Follow-up database and Seattle Angina Questionnaire completed every six months until study completion.

Data storage will be kept on a password protected non-networked computer in a password protected Filemaker-Pro database containing the elements defined above. Backups will consist of routine weekly optical backup as well as hard copy storage in the secure data archival area at the Dr. Kiran C. Patel Research Institute.

Data access will be restricted to the principal investigator, Janice Shirley and the assigned clinical research coordinator.

Hard copy data will be retained for seven years. Janice Shirley is responsible for data retention and destruction.

Data Analysis

Coronary Angiograms: Angiograms will be analyzed by Dr. Lambert documenting the presence or absence of coronary artery disease (CAD) in proximal, mid-, and distal segments of all three major coronary arteries as well as the left main artery.

Categorical data will include the presence or absence of significant disease. Specific lesions will be analyzed utilizing quantitative angiography (General Electric DMS) for continuous data including percent stenosis, minimum lumen diameter, lesion length, presence of calcification, and reference vessel diameter. Left ventricular angiography will be analyzed utilizing Simpson's rule methodology for global and regional function. Categorical data will

include normal or abnormal function and continuous data will include ejection fraction.

IVUS: Pullback images will be analyzed by Dr. Lambert in proximal, mid-, and distal segments of all three major coronary arteries as well as the left main artery.

Measurements will include EEM diameter, EEM area, vessel lumen diameter, vessel lumen area, plaque+media thickness, plaque+media area, lumen perimeter, calcium length, stenotic lesion length, lumen eccentricity index, plaque+media eccentricity index, remodeling index, lumen shape index, lumen diameter ratio, EEM diameter ratio, EEM volume, lumen volume, native plaque volume, total plaque volume, calcium distribution, lesion morphology, and plaque composition if estimable.

EBCT: Scanning and analysis will follow the methodology of the PACC Study [1]. See the EBCT section above for methods.

Framingham Risk Scores (FRS): The predicted 10-year FRS for incident CHD will be calculated using measured risk factor variables as specified within regression equations from the Framingham Heart Study [22].

NIRS: As described in validations studies, the lipid core burden index will be determine for each arterial segment interrogated (identical to IVUS segments). This index will analyzed as a continuous variable.

Statistical Analysis: The prevalence of most variables defined above has not been defined for an all-inclusive catheterization population as that used in the present study. In particular, the prevalence of NIRS detected lipid pools is unknown. Thus, sample size considerations (630) are based on those useful in the PACC study that assumes a prevalence of 23% to estimate the true prevalence (technical objective one) with a 95% confidence of ±2%.

For univariate analyses, continuous variables will be compared using the t test for independent groups and categorical variables using the chi-square test. Multivariate analysis will be performed using Cox proportional hazards modeling and stepwise methods to examine the independent predictive value of NIRS scores, CAD severity, IVUS metrics, and CAC in tertiles for adverse cardiac events. Standard forward and backward analyses will be performed.

Significance of the Research

The ability to detect vulnerable plaque and intervene with medical or mechanical therapy to prevent transition from a stable to an unstable clinical state would represent significant advancement in treatment of patients with coronary disease [23]. Application of near infrared spectroscopy to

characterization of the coronary arterial wall represents a promising approach to this problem [5].

The undetected vulnerable plaque represents a potentially catastrophic lesion in individuals with high-risk occupations. This risk stems from not only the unpredictability of plaque rupture, but also the very nature of the stressors felt to be important in this conversion. These include hemodynamic stress, mental stress, acute hormonal changes, and others [24]. Many of these potential facilitators of plaque rupture are indeed associated themselves with high-risk occupations and hazardous duty.

This project will relate the presence or absence of vulnerable plaque as detected by near infrared spectroscopy to adverse cardiac outcomes. This has special relevance to screening individuals in high-risk occupations such as aeromedical evaluation of pilots.

Duration of the Project

The initial duration of this project will be five years.

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development of vulnerable plaque. Curr Opin Cardiol, 2000. 15(6): p. 430-40.

Appendices

Screening Log

STUDY SCREENING LOG					*Check if patient excluded!*								
Patient Name	Room	Sex/Age	ABLATE AF	ALERTS	ATTRACT (DVT)	CANTOS (MI)	DEI (ACS) Examine	PRESERVE MI (Amorcyte)	RIVER PCI	SELECT-ACS (NSTEMI)	TAO (NSTEMI)	TRANSLATE-ACS	DOD

Device Specifications

CAUTION: When connected to the infraredx TVC Imaging System™, laser radiation is emitted from distal end of catheter. Do not stare into beam or view directly with optical instruments.

CAUTION: Federal law (USA) restricts this device to sale by or on the order of a physician.

WARNING: The TVC Insight™ Catheter, Controller knob, Sterile TVC Nexus Controller Barrier, and Priming Accessories are designed and intended for single patient use only. Do NOT resterilize and/or reuse the catheter. Reuse or resterilization may compromise the integrity of the device which may, cause patient injury, illness, or death. After use, dispose of the product and packaging in accordance with hospital and/or local government policy.

Catheter Description
The TVC Insight™ Catheter[1] is a single use, disposable coronary catheter designed for use only with the infraredx TVC Imaging System™.
The catheter consists of the following:

- catheter outer body with guide wire provision, radiopaque markers, and fixed hub
- torque transmission cable and core with rotating hub
- optical and ultrasound imaging core

The catheter usable length is 160 cm with 2.4Fr, 3.2Fr and 3.6Fr profiles for the tip, window and shaft, respectively. The catheter outer body is made up of a soft, atraumatic tip, a clear imaging window, and a stiffer proximal shaft. The catheter is intended to be introduced into the vasculature via a 0.014" coronary guidewire. A guidewire lumen at the distal tip of the catheter allows the catheter to track along the wire. The guidewire is allowed to exit approximately 25 mm proximal to the distal tip. A 15 cm clear imaging window is located proximal to the guidewire lumen. Two low-profile polymer markers are placed on the stiff proximal shaft to aid the user in locating the exit of the distal tip through the tip of a guiding catheter. The catheter fixed hub is affixed to the proximal portion of the catheter body.
The torque transmission cable is composed of a high torque, flexible rotating drive cable, and contains the imaging core. The catheter rotating hub is affixed to the proximal portion of the torque transmission cable. The catheter core can only be retracted, advanced and rotated when the catheter is connected to the pullback and rotation unit Controller. With the catheter fixed hub held stationary by the Controller, the rotating hub can be advanced and retracted as well as rotated. These actions impart motion to the torque cable within the sheath.
The imaging core consists of two optical fibers bonded at their distal ends to an outward looking micro-optical tip as well as a coax cable bonded to an angled ultrasound transducer. Pullback and rotation of the torque cable imparts pullback and rotation to the optical tip and transducer, causing the tip to move within the optically transparent transmission window portion of the sheath, thus scanning the artery.
The catheter contains a radiopaque marker, located approximately 5 mm from the distal end of the catheter. The catheter includes 3 mL and 10 mL or 12 mL syringes, extension line, one-way valve, and three-way stopcock (packaged separately) to flush the catheter with heparinized saline prior to use. A luer fitting on the fixed hub is used to insert saline, while a small opening at the distal end of catheter allows air to be removed.

Indications for Use
The infraredx TVC Imaging System™ is intended for the near infrared and ultrasonic examination of coronary arteries in patients undergoing invasive coronary angiography. The System is intended for the detection of lipid core containing plaques of interest (LCP). The System is intended for the assessment of coronary artery lipid core burden.

Contraindications
Use of the infraredx TVC Insight™ Catheter is contraindicated where introduction of any catheter would constitute a threat to patient safety. Contraindications include:

- Bacteremia or sepsis
- Major coagulation system abnormalities
- Severe hemodynamic instability or shock
- Patients diagnosed with coronary artery spasm
- Patients disqualified for CABG surgery
- Total occlusion
- Patients disqualified for PTCA
- Patients who are not suitable for IVUS procedures

Complications
The following complications may occur as a consequence of intravascular examination:

- Arterial dissection, injury or perforation
- Acute myocardial infarction
- Ventricular fibrillation
- Total occlusion
- Unstable angina
- Air embolism
- Abrupt closure
- Death
- Cardiac Tamponade
- Thrombus Formation

Instructions for use

Materials and Equipment
TVC Insight™ Catheter (single-use)
TVC Nexus™ Controller (Pullback/Rotation System) Knob (single-use)
TVC Imaging System™*
Sterile TVC Controller Barrier* (single-use)
Priming Accessories* (single-use)
TVC Imaging System™ User Manual*
Pre-formed guide catheter (≥ 0.067" I.D. min.)*
Rotating hemostatic valve (RHV)*
Guidewire, 0.014 inches maximum diameter*
Heparinized normal saline*

*Not packaged with catheter.

Inspection Prior to Use
Prior to use, inspect the catheter and its packaging for damage or breach of the sterile packaging seal(s). The catheter has been inspected and sterilized using Ethylene Oxide gas prior to shipment. Prior to scanning, all equipment to be used during the procedure should be carefully examined to ensure proper performance. Prior to use, ensure that the catheter has not been damaged or breached and that no particulate is present inside the catheter.

TVC Imaging System and Nexus Controller Preparation
Refer to the TVC Imaging System User Manual.

CAUTION: Do not place sharp objects, including guide wire lumen flushing tips, near the catheter imaging window.

Catheter Preparation
1. Using sterile technique, remove catheter and Controller knob from packaging.
2. Using sterile technique remove priming accessories from packaging
3. Remove the catheter from the protective hoop.
4. Fill a rinse tray with heparinized saline.

NOTE: Do NOT use any type of contrast media either in replacement of or in combination with the saline as priming medium. The use of contrast inside the infraredx TVC Insight Catheter will interfere with the pullback and rotation mechanisms of the catheter.

5. Draw three mL of heparainized saline into the 3 mL syringe and ten mL heparinized saline into the 10 mL or 12 mL syringe. Connect the 3 mL and 10 mL or 12 mL syringes to the 3-way stopcock. Connect extension line (with one way valve attached) to the 3-way stopcock.

Connecting the TVC Insight™ Catheter to the Nexus Controller™
The catheter must be connected to the TVC Nexus Controller by a sterile operator in the sterile field. However, before connecting the catheter, you must:

1. Prepare the Controller for sterile use, by covering with sterile barrier and connecting the Controller knob (Refer to TVC Imaging System User manual).

NOTE: Do not contaminate the fiber faces of the catheter or Nexus Controller during the connection process.

2. Attach the sterile purple Controller knob to the Controller unit by snapping the Controller knob into the Controller knob socket through the access point on the sterile barrier. Ensure the sterile purple Controller knob does not become entangled with the sterile barrier.

   NOTE: If sterile Controller barrier is damaged at any time, immediately replace with a new sterile Controller barrier. The sterile purple Controller knob will have to be carefully removed before removing the Controller sterile barrier. Additionally, the sterile purple Controller knob should be handled carefully since the bottom of the purple Controller knob will be non-sterile because of its contact with the non-sterile Controller mechanism.

3. Remove the blue covering from the Controller connection socket along the perforated lines and confirm that the sterile barrier socket is engaged to the Controller connection socket.

NOTE 1: The Controller Catheter Release button houses an orange and green LED (light). The orange light indicates the status of the rotary and linear axes. The green light indicates the status of the optical connections.

NOTE 2: The Controller should be positioned on the patient table such that adequate space for the Catheter connection is available and the Controller connection receptacle is free of obstructions.

4. Confirm the orange light on the **Catheter Release** button is ON. If it is blinking, then this indicates the Controller receptacle is not aligned along the linear axis and/or rotational axis. Use the PBR knob to move it to the most distal position. (The orange light is now ON.)
5. Next align the Catheter plug (its purple side up and its ribbed side facing downwards) with the Controller receptacle.
6. Firmly holding the Controller with one hand and the catheter in the other, insert the Catheter plug into the Controller receptacle. An audible clicking sound is heard and the green light is lit.

NOTE: If the green light is blinking, then there is a partial optical connection. You need to push the Catheter further into the Controller receptacle, or disconnect the Catheter and repeat Steps 4 thru 6 above.

7. Connect the free end of the priming accessory extension line to the side port on the catheter hub.
8. Retract the catheter imaging core completely to the proximal position using the controller knob.
9. Flush the TVC Insight catheter TWICE using the 3 mL syringe. Use the 10 mL or 12 mL syringe as a reservoir to refill the 3 mL syringe.

NOTE: Do NOT use excessive pressure during priming.

10. Inspect the distal end of the catheter visually for air bubbles. If air bubbles are present, flush the system with heparinized saline using the 3 mL priming syringe.
11. Refill the 10 mL or 12 mL syringe as needed and reattach to stopcock without introducing air into the system.
12. Advance the catheter imaging core to the fully distal position using the TVC Controller knob. You are now ready to perform a pullback.
13. Activate the Catheter Connection Test (CCT) and confirm proper IVUS function of the catheter. Refer to TVC Imaging System Users Guide for additional information.

CAUTION: Performing the CCT will retract the imaging core and may introduce air into the catheter body. Advance the catheter imaging core to the fully distal position using the Controller knob and flush the catheter using the 3 mL priming syringe immediately prior to catheter insertion into the patient.

NOTE: Once the Catheter is connected, due to potential linear motion of the Controller, the orange light may or may not be ON (if not ON, turn the Controller knob to the most distal position). However, in either case, as long as the green light is ON, you can still perform pullback.

Introduce Catheter into Guide Catheter and Artery

CAUTION: The TVC Insight Catheter, TVC Controller Knob, and Sterile Controller Barrier are designed and intended for single patient usage only. Do NOT resterilize and/or reuse any of these components.

1. Confirm that the catheter core is in the distal most position (the catheter release button should be illuminated ORANGE when fully distal).
2. Press the Controller knob to lock the catheter core in the distal most position.

NOTE: Advancing the Controller to the distal most position will ensure catheter trackability is optimized. Flush the catheter one more time while the imaging core is in the full distal position using the 3 mL priming syringe.

CAUTION: To prevent air from being introduced into the catheter body, DO NOT retract the imaging core prior to catheter insertion. Any amount of retraction of the imaging core will require additional flushing with the 3 mL priming syringe.

3. Backload the guidewire into the distal end of the catheter. With internal catheter core fully advanced, physician manually advances the guidewire into the catheter until the guidewire exits from the wire exit port.

NOTE: Guidewires that supply more stiffness near the distal tips are recommended.

CAUTION: Never advance the TVC Insight catheter without guidewire support
.
CAUTION: Never advance the TVC Insight catheter without the core advanced to its most distal position.

CAUTION: Never advance, or withdraw the TVC Insight catheter without direct, fluoroscopic visualization.

CAUTION: Never advance the distal tip of the TVC Insight catheter near the very floppy end of the guidewire. This part of the guidewire will not adequately support the catheter. A catheter advanced to this position may not follow the guidewire when it is retracted and cause the guidewire to buckle into a loop which the catheter may drag along the inside of the vessel and catch on the guide catheter tip. If this occurs, it will be necessary to remove the catheter assembly, guidewire and the guide catheter together. If the catheter is advanced too near the end of the guidewire, advance the guidewire while holding the TVC Insight catheter steady. If this fails, withdraw the catheter and guidewire together.

4. Advance the imaging catheter into the guide catheter, up to the femoral marker on the catheter shaft. Tighten the hemostasis valve on the guide catheter. Tighten only enough to prevent fluid / blood leakage. AN EXCESSIVELY TIGHTENED HEMOSTASIS VALVE MAY DISTORT THE IMAGE DUE TO BINDING OF THE ROTATING DRIVE CABLE.
5. With Controller rotation and pullback stopped and using fluoroscopy, advance the imaging catheter over the guidewire until the tip of the imaging catheter is beyond the region of interest (the imaging tip is the radiopaque catheter section immediately proximal to the distal radiopaque marker)

WARNING: If resistance is encountered anytime during positioning, DO NOT pull, push, or rotate with excessive force.

Catheter Imaging
The catheter body, guide catheter, and guidewire must remain fixed when imaging. Refer to the TVC Imaging System User Manual for instructions on proper use of the TVC Imaging System Console and Controller for imaging.

NOTE: Guidewires that supply more stiffness near the distal tips are recommended.

CAUTION: Never advance the TVC Insight Catheter without guidewire support.
CAUTION: Never advance or withdraw the TVC Insight Catheter without direct, fluoroscopic visualization.
CAUTION: Do not use excessive force when re-advancing the TVC Insight catheter core inside the imaging window. The core should move forward with ease.
CAUTION: Never advance the distal tip of the TVC Insight catheter near the very floppy end of the guidewire. This part of the guidewire will not adequately support the catheter. A catheter advanced to this position may not follow the guidewire when it is retracted and cause the guidewire to buckle into a loop which the catheter may drag along the inside of the vessel and catch on the guide catheter tip. If this occurs, it will be necessary to remove the catheter assembly, guidewire and the guide catheter together. If the catheter is advanced too near the end of the guidewire, advance the guidewire while holding the imaging catheter steady. If this fails, withdraw the catheter and guidewire together.

If a repeat scan is intended:
1. Withdraw the imaging catheter into the guide catheter.
2. Advance the catheter imaging core to the fully distal position using the Controller knob.
3. Confirm that the catheter core is in the distal most position (the catheter release button should be illuminated ORANGE when fully distal).
4. Press the Controller knob to lock the catheter core in the distal most position.
5. Advance the imaging catheter over the guidewire until the tip of the imaging catheter is beyond the region of interest

When done imaging, maintain the position of the guidewire and withdraw the imaging catheter. If imaging catheter is to be re-inserted, flush and coil the catheter and set aside. When ready to re-insert the catheter, re-prep the catheter as previously instructed.

NOTE: Inspect the guidewire exit port prior to re-insertion to verify that no damage has occurred during withdrawal.

Catheter Disconnection

1. Use the Controller knob to advance the Controller to the distal-most position and confirm that the orange light in the **Catheter Release** button is lit. If the orange light is not lit, then *you cannot* remove the Catheter.
2. Press and hold down the **Catheter Release** button, and then pull on the catheter hub. Do not release the **Catheter Release** button until the Catheter is completely disconnected from the Controller.

NOTE: Do not hold the Controller Knob during catheter disconnection.

Cautions and Warnings

1. Do not use the catheter if the inner package is open or damaged.
2. Do not use a catheter that has been damaged, breached or has particulate present inside.
3. Store in a cool, dry place.
4. Care should be taken when a guidewire is exposed in a stented vessel. Catheters that do not encapsulate the guidewire may engage the stent between the junction of the catheter and guidewire.

5. Ensure Controller remains level after catheter connection.
   Do not use excessive force when re-advancing the catheter core inside the imaging window. The core should move forward with ease.
6. Care should be taken when readvancing a guidewire after stent deployment. A guidewire may exit between stent struts when re-crossing a stent that is not fully opposed. Subsequent advancement of the catheter could cause entanglement between the catheter and the stent.
7. If resistance is met upon withdrawal of the catheter, verify resistance using fluoroscopy and ensure the catheter is not entangled in a stent or other interventional device then remove the entire system simultaneously.
8. **Do not kink or sharply bend the catheter at any time.** This can cause drive cable failure. An insertion angle greater than 45 degrees is considered excessive.
9. If a TVC Insight catheter sheath breach occurs during the procedure, do not advance the catheter core. Immediately remove the entire system using fluoroscopic guidance.
10. It is possible for medical waste to cause infection and/or disease. After use, dispose of product and packaging in accordance with hospital, administrative and/or local government policy.
11. This TVC Insight catheter, PBR Knob, and Sterile Controller Barrier knob are supplied sterile and are designed for single patient use only. For infection control and because of the possibility of equipment damage from Autoclave or EtO sterilization, DO NOT reuse or resterilize. Failure to heed this warning may result in serious injury or death to the patient.

Limitations

infraredx warrants that reasonable care has been used in the design and manufacture of this system. Under no circumstances shall infraredx be liable for any incidental, special, or consequential loss, damage or expense, direct or indirect, from the use of its products. User agrees to assume all liability and to be solely responsible for and to defend, indemnify and hold infraredx harmless from any claims or damages whether arising from warranty, contract or otherwise (including negligence, strict liability, and failure to warn) based on improper inspection, multiple use of single use items, selection of patients, application, operation, use and misuse of infraredx products. No agent, employee or representative of infraredx has any authority to change any of the foregoing or assume or bind infraredx to any additional liability or responsibility in connection with this device.

1. Made in USA. Patent # 6,654,630.

Nurse Follow-up

Before follow-up phone calls are made, the coordinator will check the Social Security database for death. If available, new office and/or hospital records will be obtained. Interval events will be recorded from those source documents if available.

Interview Script for Follow-up Database Form

1. Introduction: Good morning/afternoon, this is (Name) working with Dr. Lambert to see how you are doing and get some information related to the research study (abbreviated name) that you helped us with in (month). Is this a good time to talk?
2. First, I would like to ask you some brief questions from the Seattle Angina Questionnaire you completed during the hospital stay – enter into CV outcomes database.
3. Can you review your medication with me? Enter and reconcile with prior list.
4. Have you had – review list of outcomes.
5. Do you have any questions for us?
6. Thank you, I will be contacting you again – estimate date. Feel free to call me with any questions or concerns. Follow-up database form:

Patient ID		
Date of Index Procedure		
Date of Followup	Date	
Seattle Angina Questionaire Completed	Y/N	
Death From Any Cause	Y/N	Date
Cardiac Death	Y/N	Date
Other CV Death	Y/N	Date
PCI	Y/N	Date
CABG	Y/N	Date
CHF	Y/N	Date
Hospitalization	Y/N	Date
Arrhythmia	Y/N	Date
ACS	Y/N	Date
CVA	Y/N	Date
List Medications		

The Seattle Angina Questionnaire

1. The following is a list of activities that people often do during the week. Although for some people with several medical problems it is difficult to determine what it is that limits them, please go over the activities listed below and indicate how much limitation you have had **due to chest pain, chest tightness, or angina over the past 4 weeks:**

Place an X in one box on each line

Activity	Extremely Limited	Quite a bit Limited	Moderately Limited	Slightly Limited	Not at all Limited	Limited for other reasons or did not do the activity
Dressing yourself	☐	☐	☐	☐	☐	☐
Walking indoors on level ground	☐	☐	☐	☐	☐	☐
Showering	☐	☐	☐	☐	☐	☐
Climbing a hill or a flight of stairs without stopping	☐	☐	☐	☐	☐	☐
Gardening, vacuuming, or carrying groceries	☐	☐	☐	☐	☐	☐
Walking more than a block at a brisk pace	☐	☐	☐	☐	☐	☐
Running or jogging	☐	☐	☐	☐	☐	☐
Lifting or moving heavy objects (e.g. furniture, children)	☐	☐	☐	☐	☐	☐
Participating in strenuous sports (e.g. swimming, tennis)	☐	☐	☐	☐	☐	☐

2. Compared with 4 weeks ago, how often do you have **chest pain, chest tightness, or angina** when doing your **most strenuous** activities?

I have had **chest pain, chest tightness, or angina**...

Much more often	**Slightly more** often	About **the same**	**Slightly less** often	**Much less** often	I have had **no chest pain** over the last 4 weeks
☐	☐	☐	☐	☐	☐

3. Over the past 4 weeks, on average, how many times have you had **chest pain, chest tightness, or angina**?

I have had **chest pain, chest tightness, or angina**...

4 or more times per day	1-3 times per day	3 or more times per week but not every day	1-2 times per week	Less than once a week	None over the past 4 weeks
☐	☐	☐	☐	☐	☐

4. Over the past 4 weeks, on average, how many times have you had to take nitroglycerin (nitroglycerin tablets or spray) for your **chest pain, chest tightness, or angina**?

I have taken nitroglycerin...

4 or more times per day	1-3 times per day	3 or more times per week but not every day	1-2 times per week	Less than once a week	None over the past 4 weeks
☐	☐	☐	☐	☐	☐

5. How bothersome is it for you to take your pills for **chest pain, chest tightness or angina** as prescribed?

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not** bothersome at all	My doctor has **not prescribed** pills
☐	☐	☐	☐	☐	☐

6. How satisfied are you that everything possible is being done to treat your **chest pain, chest tightness, or angina**?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

7. How satisfied are you with the explanations your doctor has given you about your **chest pain, chest tightness, or angina**?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

8. Overall, how satisfied are you with the current treatment of your **chest pain, chest tightness, or angina**?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

9. Over the <u>past 4 weeks</u>, how much has your **chest pain, chest tightness, or angina** limited your enjoyment of life?

It has **extremely** limited my enjoyment of life	It has limited my enjoyment of life **quite a bit**	It has **moderately** limited my enjoyment of life	It has **slightly** limited my enjoyment of life	It has **not** limited my enjoyment of life at all
☐	☐	☐	☐	☐

10. If you had to spend the rest of your life with your **chest pain, chest tightness, or angina** the way it is right now, how would you feel about this?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

11. How often do you think or worry that you may have a heart attack or die suddenly?

I **can't stop** thinking or worrying about it	I **often** think or worry about it	I **occasionally** think or worry about it	I **rarely** think or worry about it	I **never** think or worry about it
☐	☐	☐	☐	☐

Measurement Database Input Form

Patient ID										
Date										
LV Data	Global EF	Anterolateral	Apical	Lateral	Diaphragmatic	Post-Basal	Septal			
Coronary Data										
	Left main	Proximal Anterior Descending	Mid Anterior Descending	Distal Anterior Descending	Proximal Circumflex	Mid Circumflex	Distal Circumflex	Proximal Right	Mid Right	Distal Right
Angiographic										
Diameter										
Calcification										
% Stenosis										
IVUS										
EEM Diameter										
EEM Area										
Lumen Diameter										
Lumen Area										
Plaque+Media Thickness										
Plaque+Media Area										
Lumen Perimeter										
Calcium Length										
Stenotic Lesion Length										
Lumen Eccentricity Index										
Plaque+Media Eccentricity Index										
Remodeling Index										
Lumen Shape Index										
Lumen Diameter Ratio										
EEM Diameter Ratio										
EEM Volume										
Lumen Volume										
Plaque Volume										
Calcium Distribution										
Lesion Morphology										
NIRS										
Lipid Core Burden Index										
EBCT CAC Score										

Medical Monitor

As noted earlier, specific adverse events experienced by subjects involved in this study will be reported to the site's IRB in accordance with their procedures, to the sponsor and to the Medical Monitor for the study, Dr. Michael Berlowitz (letter attached).

The SAE event reporting form for the site is attached. Reporting criteria are under A and B on the form.

FLORIDA HOSPITAL PEPIN HEART INSTITUTE
Dr. Kiran C. Patel Research Institute
The skill to heal. The spirit to care.®

Report of Serious Adverse Event – Local Protocol Deviation/Violation

Florida Hospital Tampa Bay Division IRB

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1. Contact Information

Today's Date:	Date of Initial Review:	Date of Last Review:	
Type of Submission:	☐ Serious Adverse Event[A] - Local	☐ Protocol Violation[B]	
Date of Local SAE Event:			
Protocol Title:			
Principal Investigator:			
Primary Contact:		E-mail:	
Telephone:		Fax:	

2. Current Status of Project (check only one):

☐ Currently in Progress.	***Enrolled:***	
☐ Closed to participant enrollment	On therapy/intervention: Long-term follow-up only:	

3. Report Type:

☐ Initial Report	☐ Follow-up Report	Follow-up Report #:
Subject #:	Age:	Sex:

4. Type of SAE:

☐ SAE - Hospitalized	☐ SAE - Persistent Disability	☐ SAE - Hospitalized
☐ SAE - Prolonged Hospitalization	☐ SAE - Death	

5. Type of Deviation/Violation:

☐ **Protocol Violation involving:**	☐ **Protocol Deviation involving:**	
☐ Enrollment process (I/E , recruitment)	☐ Consent process	☐ Drug / Device administration
☐ Complaint from research subject	☐ Audit finding / Monitor report	
☐ Other:		

6. Describe Event:

Principal Investigator Signature: _____ Date: _____

IRB Chair/Co-Chair Signature: _____ Date: _____

7. Relationship to Study Drug?

☐ Not Related	☐ Possible	☐ Probable
☐ Related	☐ Undetermined	

8. Relationship to Study Device?

☐ Not Related	☐ Possible	☐ Probable
☐ Related	☐ Undetermined	

9. Action Taken (select all that apply)

☐ No Action Taken	☐ Patient Continues on Study
☐ Observation	☐ Patient Discontinued from Study
☐ Dose Adjustment	☐ Patient Died
☐ Off Treatment & on Follow-up	
☐ Other Treatment (please describe):	

_____

A Reporting requirements for Serious & Unexpected AEs that occur at Florida Hospital Tampa Bay Division must be reported within 10 working days after the event is known to the investigator, or within 48 hours if the event involves a death.

Definitions:
An **Adverse Event** (AE) is any unfavorable or unintended effect on a research participant whether or not the event is deemed study-related. AEs include new or increased symptoms, diagnoses, lab results or changes to a pre-existing condition. AEs are monitored throughout the duration of a study and for a specified period after the completion of study procedures.
A **Serious Adverse Event (SAE)** includes death, life threatening events, hospitalization or prolongation of hospitalization, disability or incapacitation, overdose, congenital anomalies and any other serious events that may jeopardize the health or well-being of the subject or require medical or surgical intervention to prevent one of the outcomes listed in this definition.
An **Unexpected Adverse Events** are occurrences that were not anticipated as risks in the IRB-approved protocol and consent form, or events that occur at a greater frequency or intensity than anticipated.

B Reporting requirements for Protocol Deviation / Violation that occur at Florida Hospital Tampa Bay Division must be reported within 10 days of the principal investigator becoming aware of the deviation or violation. If not reportable, do not send to the IRB.

Deviation / Violation that affect:
Rights / welfare of subject(s) – includes errors related to informed consent form and/or process
Safety of subject(s) – subject was harmed or could have possibly been harmed.
Integrity of research data as defined by protocol and /or sponsor
Subject's willingness to continue study participation.
Non-compliance with IRB approval of study and/ or informed consent.
Non-adherence to the protocol in the absence of a waiver or exception from the sponsor.
Deviation / violation occurred to prevent apparent, immediate hazard to the subject.

Principal Investigator Signature: _____ Date: _____

IRB Chair/Co-Chair Signature: _____ Date: _____

USF HEALTH

UNIVERSITY OF SOUTH FLORIDA
COLLEGE OF MEDICINE
DEPARTMENT OF CARDIOVASCULAR SCIENCES

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For Advanced Health Care
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Tampa, Florida 33606
(813) 259-0660
Fax: (813) 259-0665

February 29, 2012

Dear Dr. Lambert,

Please consider this letter as acceptance to participate as a medical monitor for your study (TATRC #10169004) Application of Near Infrared Spectroscopy, Intravascular Ultrasound and the Coronary Calcium Score to Predict Adverse Coronary Events.

I will review all unanticipated problems involving risk to subjects or others, serious adverse events and all subject deaths associated with the protocol and provide an unbiased written report of the event. I will comment on the outcomes of the event or problem and in case of a serious adverse event or death, will comment on the relationship to participation in the study. I will indicate whether I concur with the details of the report provided by you as the principal investigator. I understand that reports for events determined by either the investigator or medical monitor to be possibly or definitely related to participation and reports of events resulting in death will be promptly forwarded to the ORP HRPO.

Sincerely,

Michael Berlowitz, M.D.
Assistant Professor of Medicine
Department of Cardiovascular Sciences
University of South Florida

FLORIDA HOSPITAL
PEPIN HEART INSTITUTE
Dr. Kiran C. Patel Research Institute
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Florida Hospital Institutional Review Board		Addendum 1.0
Policy: Risk Calculation - Research Associated Radiation Exposure		
APPROVED: 05/15/12	IRB Chair:	
REVISED:	Institutional Official:	

PURPOSE

To assess the increased risk, if any, of research related interventions involving radiation.

POLICY

01) Initial submissions that include study related interventions involving radiation exposure will be required to assess the following, in relation to the study:

a) Level of exposure
b) Level of increased risk
c) Type of risk(s)

02) The risk calculation will be assessed utilizing the following website:

http://www.xrayrisk.com/

03) The calculation will be based on the following:

a) Median age of study participants

b) Gender –

1. If known, the calculation will be based on the gender that is more likely to be enrolled.
2. If the expectation is to have a high number of both male and female enrollees, a calculation should be completed for both sexes.

Roles and Responsibilities

Dr. Charles Lambert: Principal Investigator for the study with full responsibility for its design, implementation and conduct.

Betsy Szymanski, R.N., C.C.R.C.: Research coordinator responsible for coordination of patient screening, enrollment and follow-up.

Janice Shirley, P.A., M.P.H., M.B.A.: Administrative Director of the Dr. Kiran C. Patel Research Institute responsible for study administration.

Conflict of Interest Statement

This is to certify that Dr. Charles Lambert (PI) has no financial and or material interest in the LipiScan™ System or in Infraredx Inc.

Charles R. Lambert, M.D., Ph.D., M.B.A.

FLORIDA HOSPITAL
PEPIN HEART INSTITUTE
Dr. Kiran C. Patel Research Institute
The skill to heal. The spirit to care.®

July 25, 2012

Charles Lambert, MD
Florida Hospital Pepin Heart and
Dr. Kiran C. Patel Research Institute
3100 East Fletcher Avenue
Tampa, FL 33613

RE: Full Board Initial Review: **IRB #2012-018**
Approval Status: Full Approval

Study Protocol: DOD STUDY **"Proposal 10169004 Application of Intracoronary Near Infrared Spectroscopy, Intravascular Ultrasound and the Coronary Calcium Score to Predict Adverse Coronary Events"** – *Version 5-2012*

Dear Dr. Lambert,

The Florida Hospital Tampa Bay Division Institutional Review Board (IRB) acknowledges receipt of the Initial Review for the DOD NEAR INFRARED SPECTROSCOPY research protocol. The IRB has reviewed and approved by Full Board Review, at its **July 17, 2012 meeting**, the following:

- Initial Application form dated 07/02/12
- Informed Consent form: Revised 07/02/12
- X-ray Risk Assessment – Male and Female: xrayrisk.com assessment
- Protocol: Version 5-2012
- Investigator Curriculum Vitae (CV): Charles Lambert, MD
- Investigator License: Charles Lambert, MD
- NIH Certification: Charles Lambert, MD
- Investigator List: identifies all investigator's associated with the study

Follow-Up Action

Provide the IRB with a study related budget.

- Approval not contingent upon completion of follow-up action.

Risk Assessment

The IRB assigned the following risk category to the study: Significant Risk (SR)

Reason Cited: Device trial involving an invasive procedure.

Vote Abstention

Charles Lambert, MD, Sami Elchahal, MD, and Janice Shirley, Administrative Director of Research, were not present for the final discussion and vote.

HIPAA Partial Waiver Approval

The IRB acknowledges the request for partial waiver of HIPAA to allow for subject recruitment screening.

Continuing Review Approval

The IRB has approved the research for **12 months with a 6 month Interim Report** requirement.

- Reason cited: Significant Risk device trial involving an invasive procedure.

The approval is subject to the following conditions:

1. You are required to conduct a **6 month** & **12 month** review of the research and report that review in writing to the IRB.
   Food and Drug Administration (FDA) regulation **21 CFR 56.103** requires all research to be subject to IRB review, no less than once per year. Continuing Review that does not occur prior to the end of the approval period as specified by the IRB **(see valid through date)**, results in automatic expiration of the approval **(21 CFR 56.103)**. Continuation of research after expiration of the approval can result in termination of the research **(21 CFR 56.113)**.
2. You are required to report any changes in research activity promptly to the IRB.
   In accordance with Food and Drug Administration regulation **21 CFR 56.108(a)(2)**, the IRB requires all changes in approved research to be promptly reported to, and approved by the IRB. Failure to report changes can result in termination of the research **(21 CFR 56.113)**.
3. Changes in approved research may not be initiated without IRB review and approval, except where necessary to eliminate apparent immediate hazards to the subjects.
4. You are required to promptly report to the IRB any unanticipated problems or adverse events involving risks to subjects or others.
5. When applicable **(informed consent requirement, active enrollment, re-consent requirements, etc.),** you are required to give information to subjects as part of informed consent in accordance with applicable law.
6. When applicable, you shall obtain and retain documentation of informed consent. The subject must be given a copy of the consent. **The Informed Consent must have the IRB approval stamp to be valid.**
7. You are required to submit a Final Report of Research to the IRB upon completion of the trial, including data analysis reports, publications, etc.
   Food and Drug Administration (FDA) Title 21 of the Code of Federal Regulations, part 812.150 (21 CFR 812.150) requires a Final Report of Research to be submitted to the IRB.
8. The six (6) month interim report is due: **January 16, 2013**
   This IRB Continuing Review approval is valid through: **July 16, 2013**

Informed Consent "Valid Through" Date Process:

1) The Informed Consent valid through date coincides with the Continuing Review approval period.
2) Consent forms utilized up to this date remain valid and active after expiration of the Continuing Review approval date.
3) **Participants enrolled up to this date do not need to be re-consented.**
4) Participants enrolled after the expiration date will utilize the consent form newly approved during the next Continuing Review.

Please refer to the Florida Hospital Tampa Bay Division IRB Handbook (also known as the Research Ethics Review Board Handbook) if you require further clarification of these requirements. You may also refer to Title 21 Part 56 of the Code of Federal Regulations, or to Title 45 part 46 for department of Health and Human Services studies, at the following websites:

Food and Drug Administration: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm

Health and Human Services: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm

Please note that effective September 20, 2011, the University Community Hospital Research Ethics Review Board (RERB) has changed its name to "Florida Hospital Tampa Bay Division Institutional Review Board." During the transition period in which the new name is applied to the IRB documents and/or tools, **the University Community Hospital Research Ethics Review Board document titles, approval stamps, etc., remain valid.**

An original stamped Informed Consent approved by the IRB is included for your use. If you have any questions or concerns, please contact Brenda Wright, IRB Administrator, at (813) 615-7527, or by e-mail at brenda.wright@ahss.org.

Sincerely,

08/13/2012

Wayne Taylor, PharmD Date
Co-Chair, Florida Hospital Tampa Bay Division IRB
IRB00001715
FWA00001432

Brigitte W. Shaw, COO Date
Institutional Official

WT:bw
Enclosure

INFORMED CONSENT

Name of Research Study: ***Proposal 10169004 Application of Intracoronary Near Infrared Spectroscopy, Intravascular Ultrasound and the Coronary Calcium Score to Predict Adverse Coronary Events***

Study Sponsor (Funding the Study): **Telemedicine and Advanced Technology Research Center U.S. Army Medical Research and Materiel Command Ft. Detrick, MD 21702**

Principal Investigator: Charles R. Lambert, M.D.

Sub Investigators: None

You are being asked to participate in a clinical research study sponsored by the Department of Defense. No investigational drugs or devices are being utilized in the study. **The purpose of this form is to provide you with enough information so you can understand the possible risks and benefits of participating in this study and decide whether or not you want to be part of this research study.**

This study is being conducted by Dr. Charles R. Lambert, with certain medical procedures performed at Florida Hospital Pepin Heart Institute. Florida Hospital Tampa reviews research studies through its Institutional Review Board (IRB), but is not an investigator in this study and does not supervise or direct the study.

You need to read the following material to make sure that you are informed about this study. You will have a chance to discuss any questions you have with a member of the study teambefore signing this form. Signing this form shows you have been informed, have had all your questions answered to your satisfaction and shows you give your consent to participate. If youwish to participate in this study, you must sign this form.

This consent form may contain words that you do not understand. Please ask the Principal Investigator or another member of the study staff to explain any words or information that you do not understand.

PURPOSE OF THE STUDY:
You are being invited to take part in this research study thatinvolves experimental research. The main purpose of the study is to collect information about the calcium and lipid content in your coronary arteries and to relate this to future events.

A maximum of 230 patients will be tested in this study.

PROCEDURE:
Your physician has determined that you need a cardiac catheterization. This procedure includes taking angiograms or pictures of the arteries that feed the muscle of your heart. These are the coronary arteries.

The angiograms that will be taken only show the inside or lumen of the arteries.This is a standard clinical test.

There are several other tests that are available that offer other information that maybe important in determining what happens to patients over the long term.

One of these tests is called calcium scoring (EBCT). This is also a standard clinical test. This is done in a CT scanner and is a commonly used test for screening patients for the existence of coronary artery disease or blockages in the arteries. As a part of this study, if you have not had recent calcium scan, one will be offered to you. This is optional. If you elect to have it, this can be done at your convenience but we would like to have it within 2 weeks of your cardiac catheterization. This test involves x-ray exposure that is approximately equal to a standard x-ray of your lumbar spine. This dose of X-ray exposure (16 mSv) does not increase your risk of cancer when estimated using standard calculations.

If you do not wish to participate in the EBCT part of the study, you can opt not to have that test done.

The other test that is a part of this study is done during the cardiac catheterization.

This procedure is also FDA approved and is a standard clinical test. The cost of the test will be covered by the study. It involves using a catheter that will be placed into your major coronary arteries during the catheterization. This catheter will acquire ultrasound images(IVUS) as well as near infrared images (NIRS) of your arteries. This information will be processed to measure possible hidden deposits of fat in your arteries that may not be seen by angiography.

Following the catheterization, we will continue to follow you by phone to keep track of any future issues that you may have such as procedures, medication changes, and symptoms. Ultimately, how you do over the years will be related to the calcium scores, near infrared data, and ultrasound data.

Relating the findings from the cardiac catheterization, the EBCT, IVUS and NIRS to how you do in the future is the object of this research.

It is anticipated that your participation in this study will last 3 years.

BENEFITS:
We do not know and cannot promise that you will benefit from this study. However, we anticipate that your participation in the study will give your treating physician additional information that would ordinarily not be part of a standard catheterization.This information will include a report of the IVUS and NIRS examinations and a report of the EBCT study if you opt to have that done. These reports will be sent to your treating physician(s) and included in your medical record. Additionally, the information obtained from this study may be of value to you or other patients in the future.

RISKS/SIDE EFFECTS:
Possible risks or side effects of participating in this research study includethose related to cardiac catheterization in general. These will be reviewed in detail with you as a part of informed consent for the procedure.

In addition, use of the infrared and ultrasound catheters will prolong the examination by 10 to 20 min. These catheters are placed inside of the arteries using standard technique and are FDA approved for this purpose. Any time a catheter isplaced into coronary arteries, there is an additional risk of blockage, clot formation, or other arterial damage. Care is taken to avoid such complications.

The risk of EBCT is related to X-ray exposure as noted above. This test involves x-ray exposure that is similar to a standard x-ray series of your lumbar spine. This dose of X-ray exposure (3 mSv) does not increase the risk of cancer when estimated using standard risk calculations.

ALTERNATIVE TREATMENT:
If you choose not to participate in this research study this will not affect your care in any way.

COST/COMPENSATION:
No compensation is available for this study. If you elect to participate, the cost of the near infrared and ultrasound examination as well as the coronary calcium scanning will be covered by the study.
In the event of physical injury as a result of your participation, medical care may be provided at Florida Hospital Pepin Heart Institute. If this occurs, such care will be billed to you or an appropriate third party for payment.

OTHER FINANCIAL INTEREST(S):
None

YOUR RIGHTS:
Signing this consent does not waive any of your legal rights.

You have the right to be given all important information about your treatment, the study and what you will be asked to do. You have the right to nottake part in the study. If you choose not to take part, this will not affect your treatment in any way or your relationship with your doctor. If you choose to take part, you are still free to leave the study at any time and you do not have to give a reason, but please let the Principal Investigator, Dr. Lambert,know in writing.

Once the study is completed, you have the right to access and to correct your personal data, to obtain a copy of the data collected and to object to the processing of the data. However, you may not be able to see or be told about the information recorded about you in the study record during the time the study is being conducted. When the study is complete you will be able to review the study information that is kept in your studyand medical records.

PRIVACY AND CONFIDENTIALITY OF STUDY RECORDS

All records related to this study will be kept in a secure location with restricted access.No personal identifiers will be utilized in publication or other use of results.

Representatives of the U.S. Army Medical Research and Materiel Command are authorized to review research records.

CONTACTS:
You may discuss any questions or concerns you may have at any time before, during or after

participating in this study with Dr. Charles Lambert, 813-615-7201.

This study was reviewed by the Florida Hospital Tampa Bay Division Institutional Review Board (IRB). The IRB is a group of people who review research studies to protect the study participants. If you have questions about what it means tobe involved in research, or about your rights as a research participant, you may contact a representative of the Research Department of Florida Hospital Tampa at (813) 615-7527, and you will be directed to the appropriate contact person.

Dr. Lambert is the Medical Director of the Research Department (Dr. Kiran C. Patel Research Institute) and a Professor of Medicine at the University of Floridaand Clinical Professor of Medicine at the University of South Florida

NEW FINDINGS:
Your doctor will inform you of any significant new findings which relate to your participation in this study and which may be discovered during your participation.

VOLUNTARY PARTICIPATION/WITHDRAWAL:
You are free to decide whether or not to participate in this research study. If you choose to participate, you may withdraw from this study at any time without penalty or loss of benefits to which you are otherwise entitled. You should inform your doctor in writing of your decision to withdraw as soon as possible in order to allow the orderly termination of your participation from the study.

Your doctor may decide to discontinue your participation in this study at any time.

HIPAA AUTHORIZATION TO RELEASE INFORMATION FOR RESEARCH

You have agreed to participate in the study mentionedabove and have signed a separate informed consent that explained the procedures of the study and the confidentiality of your personal health information. This authorization form will give you more detailed information about how your health information will be used and disclosed and will give permission for those uses and disclosures.

By signing this document you are agreeing to the uses and disclosures (sharing) of your personal health information as described below. You must sign this authorization tobe able to take part in the study.

What personal health information is collected and used in this study and might also be shared (disclosed)?

- Your name, address, telephone number, date of birth, social security number
- Your and your family's medical history, your allergies
- Your current and past medications or medical treatments
- The results of all medical tests performed as part of the study, physical examination results and information that you provide to members of the study team.

Who may use or disclose (share) your personal health information?

- The Principal Investigator and other his/her staff associated with the study
- Members of the Florida Hospital workforce
- The Florida Hospital Tampa Bay Division Institutional Review Board (the committee that oversees research on human subjects for the hospital)

Who may see this information?

The study sponsor also may see your health information and know your identity "Sponsor" includes any people or companies working for or with the sponsor or owned by the sponsor. They all have the right to see information about you during and after the study.

The following people, agencies and businesses may get information from us that reveals who you are:

- Doctors and healthcare professionals taking part in the study
- Doctors and healthcare professionals taking care of you
- U.S. Food and Drug Administration (FDA)
- U.S. Department of Health and Human Services (DHHS)
- Government agencies in other countries
- Government agencies that must receive reports about certain diseases
- Florida Hospital Tampa Bay Division representatives
- Florida Hospital Tampa Bay Division Institutional Review Board (IRB)
- Accreditation organizations
- Individuals and/or organizations as allowed by law

What information may be used and shared?

If you decide to be in this study, medical information that identifies you and relates to your participation will be created. This may include the following types of medical information.

- Information obtained from the procedures used to find out whether you are eligible to take part in this study. This may include physical examinations, blood and urine tests, x-rays and other procedures or tests, and any other information that you may release to us, including information about your health history.

- Information obtained in the course of the study including information about your response to any study treatments you receive, information related to study visits and phone calls, physical examinations, blood and urine tests, x-rays and other tests or procedures that may be performed, and other medical information relating to your participation in this study.

Why will this information be used and/or shared?

Information about you and your health, that might identify you, may be given to others to carry out the research study. The sponsor will analyze and evaluate the results of the study. In addition, people from the sponsor and its consultants may be visiting the research site. They will follow how the study is done, and they may be reviewing your information for this purpose.

The information may be given to the FDA. It may also be given to governmental agencies in other countries. This is done so the sponsor can receive marketing approval for new products resulting from this research. The information may also be used to meet the reporting

requirements of governmental agencies.

The results of this research may be published in scientific journals or presented at medical meetings, but your identity will not be disclosed.

The information may be reviewed by the Florida Hospital Tampa Bay Division Institutional Review Board. Other Florida Hospital representatives may review this research in their oversight and auditing roles.

It is the policy of the U.S. Army Medical Research and Materiel Command that data sheets are to be completed on all volunteers participating in research for entry into this Command's Volunteer Registry Data Base. The information to be entered into this confidential data base includes your name, address, Social Security number, study name and dates. The intent of the data base is two-fold: first, to readily answer questions concerning an individual's participation in research sponsored by USAMRMC; and second, to ensure that the USAMRMC can exercise its obligation to ensure research volunteers are adequately warned (duty to warn) of risks and to provide new information as it becomes available. The information will be stored at USAMRMC.

Representatives of the U.S. Army Medical Research and Materiel Command are authorized to review research records as part of their responsibility to protect human research volunteers. Research records will be stored in a confidential manner so as to protect the confidentiality of your information.

What if I decide not to give permission to use and give out my health information?
By signing this consent form, you are giving permission to use and give out the health information listed above for the purposes described above. If you refuse to give permission, you will not be able to be in this research.

How long will this authorization to use and disclose your personal health information last?
This authorization for use and disclosure (sharing) of your personal health information for this specific study will last 7 years.

Will you be able to see your study-related record?
You will be able to see your study-related record when the study is completed. Your ability to see your Florida Hospital medical record, if applicable, will be the same as if you had not signed this form.

Can you change your mind?
You may take back your permission for the use and sharing of any of your personal information for research, **but you must do so in writing** to the Principal Investigator at 3100 E. Fletcher Ave., Tampa, Florida 33613. However, even if you take back your permission, the Principal Investigator for the research study may still use your personal information that was collected before you took back your authorization if that information is necessary to the study. Also, if you take back your permission to use your personal health information that means you will be taken out of the research study.

You will be given a copy of this form.

By signing this form I am agreeing to the uses and disclosures of my personal health information as described above.

CONSENT:
I have read and understand the above information. I have been given the opportunity to ask questions, and my doctor has answered any questions I had about this research study. Based upon this information, I agree to participate in the ***Application of Intracoronary Near Infrared Spectroscopy, Intravascular Ultrasound and the Coronary Calcium Score to Predict Adverse Coronary Events*** research study.

I have been told that I will receive a signed copy of this consent form.

_____I do not wish to participate in the EBCT portion of the study
(Initial)

_____ _____/_____/_____
(Print participant name) (Date*: day /month/ year)

_____ _____
(Signature of participant or legal representative) Print name of legal representative

_____
(Description of the authority of the legal representative to act for the patient, if applicable)

_____
(Print Witness name, if required)

_____ ____/_____/_____
(Witness' Signature, if required) (Date*: day /month/ year)

I have fully discussed this research study with the patientusing a language that is appropriate and understandable. I believe that the patient understands the nature of this study and the possible risks and benefits involved in participating. I certify that I have encouraged the patient to ask questions and that all questions asked were answered.

_____
(Print Investigator or designee name)

_____ ____/_____/_____
(Signature of Investigator or designee) (Date*: day /month/ year)

* date should be completed by each person completing the signature line

Revised 08/17/12

Application of Near Infrared Spectroscopy, Intravascular Ultrasound and the Coronary Calcium Score to Predict Adverse Coronary Events

Milestones	Spending Plan
Year One • Hire new personnel dedicated to the project • Acquire NIRS console • Train staff and physicians • Establish inventory of associated supplies • Establish image archival system and database • Implement standard operating procedures • Enroll patients with a total target of 230 • Outcomes follow-up on enrolled patients • Ongoing data analysis	Initial equipment outlay and salary support as established in budget
Year Two • Enroll patients with a total target of 230 • Outcomes follow-up on enrolled patients • Ongoing data analysis • Interim analysis	Continued catheter expense and salary support proportional to recruitment. Meeting expense.
Year Three • Enroll patients with a total target of 230 • Outcomes follow-up on enrolled patients • Ongoing data analysis • Interim analysis	Continued catheter expense and salary support proportional to recruitment. Meeting expense.
Year Four • Outcomes follow-up on enrolled patients • Ongoing data analysis • Interim analysis	Continued catheter expense and salary support proportional to recruitment. Meeting expense.

FEDERAL FINANCIAL REPORT

(Follow form instructions)

1. Federal Agency and Organizational Element to Which Report is Submitted	2. Federal Grant or Other Identifying Number Assigned by Federal Agency (To report multiple grants, use FFR Attachment)	Page	of
Department of Defense	W81XWH-11-1-0831	1	1 pages

3. Recipient Organization (Name and complete address including Zip code)
University Community Hospital, Inc dba Florida Hospital - 3100 E Fletcher Ave. Tampa, FL 33613

4a. DUNS Number	4b. EIN	5. Recipient Account Number or Identifying Number (To report multiple grants, use FFR Attachment)	6. Report Type	7. Basis of Accounting
809875540	59-1113901	Bank of America Account 4427217537	☐ Quarterly ☐ Semi-Annual ☉ Annual ☐ Final	☒ Cash ☒ Accrual

8. Project/Grant Period From: (Month, Day, Year)	To: (Month, Day, Year)	9. Reporting Period End Date (Month, Day, Year)
September, 26, 2011	October, 15, 2012	August 31, 2012

10. **Transactions**	Cumulative
(Use lines a-c for single or multiple grant reporting)	
Federal Cash (To report multiple grants, also use FFR Attachment):	
a. Cash Receipts	699,000.00
b. Cash Disbursements	
c. Cash on Hand (line a minus b)	699,000.00
(Use lines d-o for single grant reporting)	
Federal Expenditures and Unobligated Balance:	
d. Total Federal funds authorized	
e. Federal share of expenditures	
f. Federal share of unliquidated obligations	
g. Total Federal share (sum of lines e and f)	
h. Unobligated balance of Federal funds (line d minus g)	
Recipient Share:	
i. Total recipient share required	
j. Recipient share of expenditures	
k. Remaining recipient share to be provided (line i minus j)	
Program Income:	
l. Total Federal program income earned	
m. Program income expended in accordance with the deduction alternative	
n. Program income expended in accordance with the addition alternative	
o. Unexpended program income (line l minus line m or line n)	

	a. Type	b. Rate	c. Period From	Period To	d. Base	e. Amount Charged	f. Federal Share
11. Indirect Expense							
				g. Totals:			

12. *Remarks: Attach any explanations deemed necessary or information required by Federal sponsoring agency in compliance with governing legislation:*

13. Certification: By signing this report, I certify that it is true, complete, and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent information may subject me to criminal, civil, or administrative penalities. (U.S. Code, Title 18, Section 1001)

a. Typed or Printed Name and Title of Authorized Certifying Official	c. Telephone (Area code, number and extension)
	d. Email address
b. Signature of Authorized Certifying Official	e. Date Report Submitted (Month, Day, Year)
	14. Agency use only:

Standard Form 425
OMB Approval Number: 0348-0061
Expiration Date: 10/31/2011